POSITION PAPER

Specific recommendations for PROs and HRQoL assessment in allergic rhinitis and/or asthma: a GA²LEN taskforce position paper

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To cite this article: Braido F, Bousquet PJ, Brzoza Z, Canonica GW, Compalati E, Fiocchi A, Fokkens W, Gerth van Wijk R, La Grutta S, Lombardi C, Maurer M, Pinto AM, Ridolo E, Senna GE, Terreehorst I, Todo Bom A, Bousquet J, Zuberbier T, Baiardini I. Specific recommendations for PROs and HRQoL assessment in allergic rhinitis and/or asthma: a GA²LEN taskforce position paper. *Allergy* 2010; **65**: 959–968.

Keywords
asthma; health-related quality of life; patient-reported outcomes; rhinitis.

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Accepted for publication 19 March 2010

DOI:10.1111/j.1398-9995.2010.02383.x

Edited by: Marek Sanak

Abstract

The GA²LEN taskforce on Patient-Reported Outcomes (PROs) and Health-Related Quality of Life (HRQoL) published in 2009 a position paper concerning PROS and HRQoL assessment in clinical trials on allergy. Because of the specificity of this topic in asthma and rhinitis, specific recommendations are needed. The aim of this position paper is to define PROs and their meaning in asthma and rhinitis research, explore the available tools to provide criteria for a proper choice, identify patient-related factor which could influence PROs assessment, define specific recommendations for assessment, analysis and results spreading, underline the unexplored areas and unmet needs. PROs assessment is gaining increasing importance, and it must be performed with a rigorous methodological procedure and using validated tools. This approach enables to better understand patient-related factors influencing clinical trials and real-life management outcomes, identify patients subgroups that can benefit from specific treatment and management plan and tailor treatment to address PROs (not only physician-defined targets) to improve asthma and rhinitis management.

Background

The expression 'Patient-Reported Outcomes' (PROs), which came into frequent use only in the last decade, refers to 'any report coming from patients about a health condition and its treatment' (1) as opposed to data provided by other sources (clinical and instrumental tests, providers and caregivers). PROs are gaining increasing awareness and emphasis in clinical research and by regulatory bodies because of their relevance in the overall treatment efficacy assessment (2, 3).

Among PROs, Health-Related Quality of Life (HRQoL) and patient-reported symptoms have been extensively evaluated in rhinitis and asthma, but unexplored areas and methodological limits have recently been identified and discussed

Abbreviations
HRQoL, Health-Related Quality of Life; MID, Minimal Important Difference; PROs, Patient-Reported Outcomes.

(4, 5). Following the consensus reached by the GA^{2}LEN task force for PROs assessment providing general criteria concerning PROs definition, meaning and methods of evaluation (e.g. choice of the tool, assessment schedule, results analysis) in allergic diseases research (6), the aim of this position paper is to provide a comprehensive collection of specific suggestions and recommendations for a proper PROs investigations into rhinitis and asthma, especially clinical trials.

Definition and relevance of PROs and PROs influencing factors in allergic rhinitis and/or asthma

The development of PROs instruments has a long history dating back to the World Health Organization's broadened definition of health as 'a state of physical, mental, and social well-being and not merely the absence of disease' (7). This statement led to the groundwork for conceptualizing health as multidimensional and served to draw the attention away from the disease-centred approach, which emphasizes physiological indices of health, towards a patient-centred approach, which includes the patient's viewpoint in evaluating the impact of an illness. Furthermore, the fundamental role of patient's perspectives is now underlined by the GRADE system (8), which represents the best option in defining the criteria for grading evidence and developing guidelines. As a matter of fact, it includes also patients' preferences and values as cornerstones in the process of formulating recommendations towards diagnostic and therapeutic interventions, thus contributing to bring scientific research to real life.

The definition of the most important PROs in scientific research on patients suffering from asthma and/or rhinitis with an example of the tools used for their assessment is reported in Table 1.

Like in other conditions, PROs in patients with asthma and rhinitis are not only influenced by factors connected to the disease itself (clinical characteristics, symptoms, severity, chronicity, comorbidities) or by therapeutical strategies adopted for their control (i.e. drug and treatment schedules) but also by variables related to the patient, both to his personal (age, sex, job, school functioning, race/ethnicity, sociodemographic characteristics and lifestyle) and psychological characteristics. Psychological factors could be considered PROs when they refer to the disease impact on the psychological factor itself (e.g.: effect of uncontrolled asthma on mood or emotional and social functioning) (70) or a patient-related factor influencing PROs when the presence of a psychological characteristic could influence PROs (e.g.: the effect of depression on asthma) (71).

Table 2 sums up some of the most relevant psychological patient-related factors influencing PROs and examples of the most suitable tools to assess them.

Among the variables reported in Table 2, mood disorders and anxiety, especially for what concerns patients with asthma, are those which deserved more attention in the respiratory allergy research (72–76). As psychological factors could influence answering to PRO tools, a proper evaluation and their introduction among trial's inclusion/exclusion criteria is suggested.

Available tools for assessing PROs in patients with rhinitis and/or asthma in clinical trials and criteria for the choice of the proper tool

For the evaluation of satisfaction, preferences, illness perception, willingness to pay and adherence, some validated questionnaires (See Table 1), already used for other diseases as well, are available. So far, many of them have not been extensively used in respiratory field, and their use is suggested for further research.

Health-related quality of life, symptoms and control assessment deserve particular considerations.

HRQoL assessment

Several validated tools for assessing HRQoL in rhinitis and asthma are currently available. In the choice of the tool, the following aspects should be considered:

Disease target

The tool should be suitable for the clinical pattern under investigation. In particular, specific tools for HRQoL assessment in asthma (12, 77–92), rhino-conjunctivitis (93–96) rhino-sinusitis (97–99), concomitant asthma and rhinitis (14, 100), specific symptoms related to asthma and rhinitis, such as cough, (101–103) or specific functional aspects (e.g. HRQoL in patients with obstructive lung disease) (104–106) are available.

The impact of conjunctivitis on patients' life, a phenomenon often investigated by specific tools for rhinitis, can also be evaluated through *ad hoc* questionnaires (107) or validated tools for specific ocular pathologies (e.g. keratoconjunctivitis) (108).

Some tools are specifically addressed to investigate the impact of pathology not on the patient but in his/her caregiver, while others refer to the child's HRQoL but are filled in by caregivers (86, 88, 91).

Population target

The tool should be chosen taking into account the range of age for which it has been specifically validated. Most of questionnaires have been developed and validated for adult patients; nowadays, specific questionnaires which investigate the obstructive pathology in the lower airways (12, 14, 77–83, 104–106), rhino-conjunctivitis (93, 95, 96, 107), rhino-sinusitis (97–99) and cough (101–103) in adult population are available. For the evaluation of HRQoL related to respiratory allergy in paediatric population, some tools which investigate asthma in children (84–88, 90, 92) and adolescents (89, 90), as well as rhino-conjunctivitis (94) and asthma with concomitant rhinitis (100), exist.

Methods of administration (*self-administered and/or interview/telephone administered*) *and format* (*paper or electronic version*)

In some paediatric tools, the answers are given in the form of smiley faces (90), and the questionnaires can be filled in with the caregiver's help (90–92).

Table 1 Definition of PROs and examples of validated tools

PRO	Definition	Examples of tools
Quality of Life (QoL)	Individual's perception of his/her position in life in the context of the culture and value systems in which he/she lives and in relation to his/her goals, expectations, standards and concerns. It is a broad-ranging concept incorporating in a complex way the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of the environment (9)	WHOQOL-100 (10)
Health-Related Quality of Life (HRQoL)	The impact of the disease and its therapy upon a patient, as perceived by patient himself (11)	Asthma Quality of Life Questionnaire – AQLQ(S) (12) Rhino-conjunctivitis Quality of Life Questionnaire – RQLQ(S) (13) RHINASTHMA (14)
Health status	The ability of a subject to function in a variety of physical, emotional and social activities (15, 16)	Medical Outcome Study Short Form Health Survey (SF-36) (17) Nottingham Health Profile (18) Quality-adjusted life year' (QALY) (19) Standard gamble (19, 20) Time trade-off (20)
Well being	An individual's evaluation of his/her health daily functioning, happiness and welfare (21)	Psychological General Well-Being (PGWB) (22)
Satisfaction	The cognitive product of the comparison between ideal life and reality and can therefore be quantitatively measured (23)	Satisfaction Profile (SAT-P) (24) SATQ (25)
Adherence	The extent to which a person's behaviour, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider (26, 27)	Medication Adherence Report Scale for Asthma (MARS-A) (28) ASK-20 (29)
Illness perception	The personal model or representation of an illness aimed at making sense and respond to the presence of a disease (30, 31)	Revised Illness Perception Questionnaire (IPQ-R) (32)
Willingness to pay	The maximum value people are willing to pay to attain a service rather than do without it (21)	Dichotomous (33) or multiple choices assessment (34) contingent evaluation question (35)
Preferences	Action that a patient would choose in a particular medical situation at a particular time, given a set of alternatives (36)	Clinical Trial Patient Preference Instrument (37) Clinical Practice Patient Preference Instrument (37) Autonomy Preference Index (38)
Symptoms	The subjective experiences about the illness, disease or injury. This experience is reported but not necessarily observed by anyone other than the patient (39)	Rhino-conjunctivitis and asthma symptom score (40) Visual analogue scale for rhinitis (41)
Control	Asthma: none (twice or less/week) daytime symptoms, none limitations of activities, none nocturnal symptoms/awakenings, none (twice or less/week) need for reliever/ rescue treatment, normal lung function, none exacerbations. (42) Rhinitis: a definition of controlled rhinitis is not preset in ARIA guidelines (43). The acronyms SCUAD (severe chronic upper airway diseases) defines those patients whose symptoms are inadequately controlled despite adequate (i.e. effective, safe, and acceptable) pharmacologic treatment based on guidelines (44)	Asthma Control Test (ACT) (45) Asthma Control Questionnaire (ACQ) (46) 'Control of Allergic Rhinitis and Asthma Test' (CARAT) (47, 48)
Work productivity	Costs associated with production Loss and replacement costs because of illness, disability and death of productive persons, both paid and unpaid (49)	Work Productivity and Activity Impairment (WPAI) (50) Work Productivity and Activity Impairment Questionnaire – Allergy Specific (WPAI-AS) (51)

Table 2 Definition of patient-related factors that influence PROs and examples of validated tools

Patient-related factors that influence PROs	Definition	Examples of tools
Alexithymia	Cluster of characteristics implying difficulties in identifying and expressing feelings, an absence of fantasy and a concrete, externally oriented thinking style, and also difficulties differentiating between emotions and bodily sensations (52)	Toronto Alexithymia Scale (TAS-20) (53, 54)
Coping	Coping strategies refer to the specific efforts, both behavioural and psychological, that people employ to master, tolerate, reduce, or minimize stressful events (55)	Coping Orientations to Problem Experienced (COPE) (56) Coping with a Disease (CODI) (57)
Locus of control	Generalized belief regarding the extent to which life outcomes are controlled by an individual's actions (internal control) or by external forces such as luck, fate or other individuals (external control) (58)	Multidimensional health locus of control (MHLC) (59) Rotter's 29-item Locus of Control (58, 60)
Personality	A dynamic organization, inside the person, of psychophysical systems that create a person's characteristic patterns of behaviour, thoughts and feelings (61)	Minnesota multiphasic personality inventory – 2 (62) Big Five Inventory Personality Test (63)
Mood disorders	The term given for a group of diagnoses in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV TR) classification system where a disturbance in the person's mood is hypothesized to be the main underlying feature (64)	Beck Depression Inventory (BDI) (65) Hospital Anxiety and Depression Scale (HADS) (66)
Anxiety disorders	A blanket term covering several different forms of abnormal and pathological fear and anxiety (64)	State-Trait Anxiety Inventory (67) Hospital Anxiety and Depression Scale (HADS) (66)
Stress	The response of the body to any demand. The term distress is used for the consequences of the failure to respond appropriately to emotional or physical threats to the organism. It includes a state of alarm and adrenaline production, short-term resistance as a coping mechanism and exhaustion. Common stress symptoms include irritability, muscular tension, inability to concentrate and a variety of physical reactions (68)	POMS (69)

A parameter to be considered when choosing a tool is also the number of items. It ranges from less than 20 items (88) to more than 70 (87, 106). Some tools, in addition to the entire version, are also available in a validated shortened version (96, 99, 109, 110).

Availability of a validated version of the tool in the studied population's language

Most of the tools are developed and validated in English (UK, USA, Canada, Australia), but others have originally been developed in German (87, 104, 105) and Italian (14, 101, 108). For some tools (e.g. 14, 78, 80–82, 92–97, 107), validation in languages different from the original is available.

Investigated dimensions

The different questionnaires, despite being specific for the same disease, are not interchangeable. Actually, they analyse different aspects of the same disease and, therefore, they provide information on different dimensions of subjectivity. For example, some questionnaires have a specific domain for sexual life (77, 104), others for sport (77), others for sleeping (77, 93, 95, 107). Therefore, the tools must be selected to match the objective of the study.

Scaling and scoring system

Tools differ for scaling and scoring system. Although it is not a major reason to choose an instrument, it should be known and taken into account both during the choice phase (i.e. to avoid the floor and ceiling effect and potential difficulties when filling in a questionnaire) and for a correct result analysis.

Most tools use a 3-point (77, 108), 4-point (84, 85, 87, 99), 5-point (14, 78, 82, 85, 86, 88, 90, 97, 101), 6-point (98, 107) or 7-point (81, 89, 91, 92, 96, 100, 102, 104, 105) Likert scale, dichotomous items (79) or a combination of a Likert scale and dichotomous items (106).

The tools also differ in the scoring system, which can include the score standardization at 100 (14, 78, 86, 88, 101, 106–108), the addition of the total score and/or the single

domains (79, 85, 87, 89, 93, 97, 98, 102–105) and mean scores (12, 77, 81, 84, 91–96, 99, 100), the multiplication by a constant factor (82).

For some questionnaires, the paper which describes the validation process does not provide information concerning the scoring calculation instructions (80, 83, 90).

The minimal important difference (MID) is an important parameter for determining sample sizes and for interpreting statistically significant PRO results in clinical trials. It was defined as the smallest change in an outcome measure perceived as beneficial by patients or physicians, which leads to a change in the patient's management, assuming minimal toxicity and cost (111, 112). MID is available for some HRQoL questionnaires (e.g. 80, 81, 92–94, 107), but it is important to remember that the MID may vary by population and context, and no one MID may be considered valid for all study applications involving a PRO instrument. Responsiveness (the ability of the questionnaire to detect significant differences over time in patients whose status has changed) (113) and MID must be demonstrated and documented for the particular study population (114, 115).

Symptoms assessment

Both asthma and rhinitis symptoms are extensively assessed in clinical trials through the use of symptoms scores that have never undergone validation process. Therefore, the use of tools whose validity, responsiveness and reliability have been evaluated (40, 41) should be encouraged.

When the PROs assessment is carried out using a symptom score (i.e. T4SS, T5SS, asthma symptoms score), the reasons for the choice should be declared in the study methods.

Disease control assessment

Control assessment is possible in asthma through different validated tools, whose characteristics do not make them interchangeable. For instance, the Asthma Control Test (ACT) (45), the Asthma Control Questionnaire (ACQ) (46) and the Lara Asthma Symptom Scale (LASS) (116) all provide a control level measurement, but while ACT and LASS only require patient's subjective evaluations, ACQ, in its original version, combines subjective symptoms, bronchodilator use and percentage of predicted FEV1. The Asthma Control Scoring System (ACSS) (117) also combines a clinical score (self-reported by the patient), functional data (which include PEF, FEV1 and delta PEF) and an inflammatory score (% sputum eosinophilia).

In children and adolescents, the efficacy of the treatment in inducing control can be assessed also with the Asthma Therapy Assessment Questionnaire (ATAQ) (118), which explores the symptoms control, behaviour and attitude barriers, self-efficacy barriers and communication gaps.

A paper describing the development process of the Control of Allergic Rhinitis and Asthma Test (CARAT) for the control evaluation in patients with asthma and rhinitis has been recently published (47, 48). Additional studies that provide data about the psychometric properties of the questionnaire and its applicability in clinical trials are needed.

Methodological issues for PROs evaluation in rhinitis and asthma clinical trials

The evidence-based medicine (EBM) recognizes that many aspects of medical care depend on individual factors, which only in part may be subject to scientific appraisal. However, the concrete effort of applying the scientific methods of investigation to PROs in rhinitis and/or asthma clinical trials should follow the rigorous and systematic approach of the EBM. To ensure the best prediction of estimates, randomized and controlled settings represent the best opportunity to evaluate PROs as primary outcomes.

Factors influencing PROs (e.g. alexithymia, illness perception) should to be taken into account in the inclusion and exclusion criteria.

The methodological rigour used for traditional outcomes measures (e.g.: biological, clinical and functional parameters) is necessary also when assessing the PROs investigated subjective variables.

PROs must be evaluated by validated tools exploring the patient's perceptions related to the outcome: each questionnaire can be demonstrated to be reliable, valid and responsive through a rigorous validation process that consists in well-defined steps (1, 114). The measurement characteristics are widely accepted and considered essential for assuring that a PRO instrument is meaningful to patients and clinicians and provides accurate and valid assessment of the intended outcomes (1).

If the trial is addressed to investigate the efficacy of a drug, a double-blind randomized controlled trial is recommended.

The length of a trial is determined by the nature of the disease (intermittent or persistent); however, the length should also be in line with the investigated PROs. As HRQoL tools provide information on patients' HRQoL during the previous 2–4 weeks, a periodical assessment of HRQoL, respecting the tool recall period, may provide a more comprehensive evaluation of the patients' perspective evaluation. According to European Medication Agency (EMEA) recommendations for medicinal products evaluation, 2- to 4-week trials for intermittent and 3- to 6-month trials for persistent diseases are suggested (3).

In trials assessing specific effects of an intervention, the choice of the PROs tool will depend on the expected intervention effects. Whenever available, a specific tool for assessing a single outcome (e.g. effect on sleep) should be used. The choice of recall period should not only depend on the type of tool but also on the expected time of appearance of the effects of the intervention under investigation (e.g. a shorter recall for symptomatic treatment than for treatment aimed at modifying the natural disease history or at reducing the disease exacerbations). A shorter recall period is expected in symptoms evaluation rather than in HRQoL assessment.

The presence of rhinitis in patients with asthma should be carefully taken into account when choosing the tool/s. When

the patient has both rhinitis and asthma, a tool for the combined HRQoL assessment of asthma and rhinitis (e.g. RHINASTHMA) (14) should be used. Alternatively, asthma and rhinitis should be simultaneously assessed (i.e. AQLQ, RQLQ) (81, 93).

As of now, we lack consistent evidence that supports the use of any PROs validated tool over another for the assessment of intermittent/persistent, mild/moderate/severe rhinitis and asthma.

As HRQoL assessment provides information on the impact of the disease but also of its intervention upon patient's life, it is necessary to consider not only the functional and clinical parameters but also the ongoing treatment. The five steps for asthma classification proposed by the Global Initiative for Asthma guidelines (42), taking into consideration the therapy necessary to achieve control, seem to be suitable. This is still missing for rhinitis (43).

In the assessment of HRQoL in intermittent/persistent, mild/moderate/severe rhinitis and asthma, the use of specific questionnaires should be preferred to the use of generic tools (5, 119).

When the impact on HRQoL of a specific symptom (such as cough) needs to be explored, disease-specific questionnaires should be used together with a symptom-specific tool (for instance, CCIQ, LCQ, CQLQ are specific tools for cough-related QoL assessment) (101–103). An overview of essential steps and issues for PROs assessment in clinical trials is shown in Fig. 1.

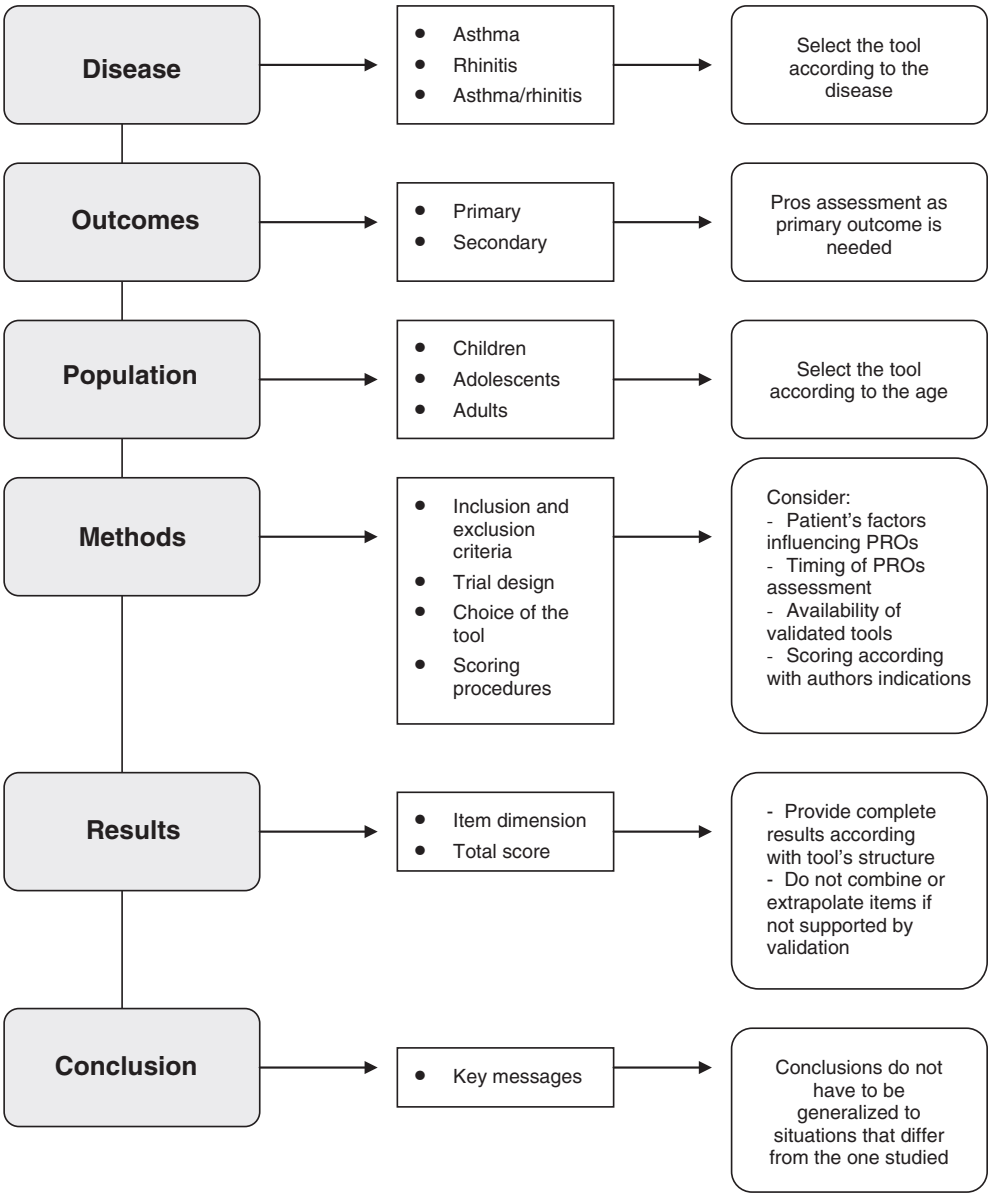

Figure 1 Essential steps and issues for PROs assessment in clinical trials.

Unexplored and unmet needs in PROs assessment in rhinitis and asthma

Although PROs assessment is relevant for a more comprehensive description of the disease and its treatment from patients' perspective and some evidences have been achieved in previous studies, the following unexplored areas should be further investigated:

- Assessment of other PROs besides HRQoL and symptoms.
- Development of tools that evaluate rhinitis comorbidities besides asthma and asthma comorbidities besides rhinitis.
- A more extensive assessment of PROs in comparison/relation with/to other clinical measures of health impact assessment.
- A more advanced PROs assessment in paediatric age, in particular the need for more efficacious targeted treatments for those paediatric patients with severely impaired disease and the need to demonstrate longitudinal factorial invariance.
- A more extensive PROs assessment besides HRQoL in caregivers/parents of rhinitic and asthmatic children.
- A rhinitis classification, taking into consideration the therapy necessary for control achievement, needs to be developed.
- Assessment of PROs as indicators of the effects of adaptation measures for modifiable risk factors (e.g. willingness to pay).

Acknowledgments

Authors thank ARMIA (Associazione Ricerca Malattie Immunologiche e Allergiche) and ASPADIRES (Associazione Disturbi Respiratori nel Sonno).

Authors acknowledge Dr Marianna Bruzzone for linguistic assistance with the manuscript.

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